REMARKS

The Present Invention

The present invention pertains to a lymphocyte having dual antigen-specificity, compositions comprising the same, a pharmaceutical composition comprising the same, and a method of preparing the same.

The Pending Claims

Claims 1, 3, 4, 6-8, 10, 11, 40, 41, and 44-70 are pending. Claims 1, 3, 4, 6-8, 10, and 44-46 are directed to a composition comprising a lymphocyte having (i) a chimeric receptor or a T-cell receptor and (ii) an endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte. Claims 11 and 47-50 are directed to a lymphocyte having a T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte, and a chimeric receptor reactive with a tumor antigen. Claims 40 and 51-55 are directed to a pharmaceutical composition comprising a lymphocyte containing a chimeric receptor and an endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte. Claims 41 and 56-61 are directed to a method of preparing lymphocytes having dual antigen specificity. Claims 62-67 are directed to isolated or purified human lymphocytes of the present invention. Claims 68, 69, and 70 are directed to a composition comprising the human lymphocyte, a pharmaceutical composition comprising the same, and a method of preparing the human lymphocytes having dual antigen specificity, respectively.

The Final Office Action

The Office has alleged that claim 5 is directed to a nonelected invention. The Office has further alleged that the instant application should claim priority to either U.S. Application No. 08/854,723 (the '723 application) or U.S. Application No. 08/547,263 (the '263 application). The Office has asserted that the status of U.S. Application No. 08/547,263, which is cited on page 17, line 5, will need to be updated prior to the allowance of the instant application. The Office has maintained the rejection of claims 1, 3, 4, 6-8, 10-12, 15, 40, 41, and 43 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office has also maintained the rejection of claims 1, 3, 6-8, 10-12, 15, 40, 41, and 43 under 35 U.S.C. § 102 (e) as allegedly anticipated by U.S. Patent No. 5,830,755 (the '755 patent). Reconsideration is hereby requested.

The Amendments to the Claims

Claim 5 has been cancelled as drawn to a non-elected invention. Claims 12, 15, and 43 also have been cancelled. Applicants reserve the right to pursue any cancelled subject matter in a continuation, continuation-in-part, divisional, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter.

Claim 1 has been amended to delete the phrases "preselected population of" and "a preselected strong antigen, wherein the preselected strong antigen is an allogeneic agent." Claim 1 has further been amended to recite "a lymphocyte comprising (i) a chimeric receptor or a T-cell receptor, either of which is reactive with a tumor antigen, and (ii) an endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte," which is supported by Examples 3-8 in the specification, for instance. Claim 3 has been amended in view of the amendment to claim 1. Specifically, claim 3 now recites "wherein the lymphocyte is a T cell." Claim 4 has been amended to delete the phrase "derived from an ovarian cancer" and has further been amended to recite "is an ovarian tumor antigen," which is supported by Examples 4-8 in the specification, for instance. In claim 6, a comma has been inserted after "claim 1." Claim 7 has been amended to recite "comprises" in lieu of "is" as supported by Figure 1, for instance. Claim 8 has been amended to recite "cell is a peripheral blood mononuclear cell," instead of "strong antigen comprises allogeneic peripheral blood cells." The recitation of "peripheral blood mononuclear cell" is supported by the specification at, for instance, pages 31 and 32, lines 4 and 5 of paragraph 81. Claim 10 has been amended to correct an obvious typographical error, i.e., to recite "Mov-γ," instead of "Mov-y." Claim 10 has also been amended to be dependent on claim 4, which is supported in the specification at, for example, page 30, lines 8 and 9 of paragraph 79. Claim 11 has been amended to recite "a cell, which is allogeneic to the lymphocyte," in lieu of "an allogeneic agent," as supported by Examples 3-8 of the specification, for instance. Claim 40 has been amended to recite "a lymphocyte," instead of "a population of lymphocytes." Claim 40 also has been amended to recite "an endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte," instead of "preselected for reactivity with a strong antigen, wherein the strong antigen is an allogeneic agent," as supported by Examples 3-8 of the specification, for instance. Claim 41 has been amended to recite "lymphocytes having dual antigen specificity," in lieu of "preselected dual specificity," which is supported by the specification at, for instance, page 31, line 12 of paragraph 80, and page 31, line 3 of paragraph 81. Claim 41 also has been amended to recite "contacting lymphocytes with a cell, which is allogeneic to the lymphocytes," in lieu of "selecting for lymphocytes

reactive with a strong antigen *ex vivo*, wherein the strong antigen is an allogeneic agent," as supported by Examples 4-8 of the specification, for instance. Claim 41 has been further amended to recite "encoding a chimeric receptor." No new matter has been added by way of these amendments.

Claims 44-70 have been added. Claims 44, 49, 55, and 60 are supported by the specification at, for instance, page 30, lines 8 and 9 of paragraph 79. Claims 45, 47, 52, and 61 are supported by Examples 7 and 8 of the specification, for example. Claims 46, 50, 56, and 58 are supported by the specification at, for example, page 29, lines 7-13 of paragraph 77, and page 30, line 3 of paragraph 79, and Examples 7 and 8. Claims 48, 54, and 59 are supported in the specification, at for instance, page 30, lines 8 and 9 of paragraph 79. Claims 51, 53, and 57 are supported by the specification at, for example, page 27, lines 1-4 of paragraph 75. Claims 62-70 are supported by Examples 7 and 8 of the specification, for instance. No new matter has been added by way of these amendments.

Discussion of Priority

The Office has asserted that the instant application repeats a substantial portion of the '263 application and adds and claims additional disclosure not presented in the prior application. In this regard, the Office has speculated that the instant application is a continuation-in-part of the '263 application. The Office has further speculated that the instant application is a divisional application of the '263 application. However, neither scenario is the case. The instant application is neither a continuation-in-part nor a divisional application of the '263 application. Therefore, the priority of the instant application is correct in that it does not claim priority to any pending parent applications.

Discussion of the Specification

The Office has alleged that the status of the '263 application, which is cited on page 17, line 5, of the instant specification, will need to be updated prior to allowance of the instant application. According to the Patent Application Information Retrieval (PAIR) system available at the U.S. Patent and Trademark Office website, the status of the '263 application is that it is on appeal. Therefore, the instant specification does not need to be amended to update the status of the '263 application at this time.

Discussion of the Rejection under U.S.C. § 112, second paragraph

The Office has maintained the rejection of claims 1, 3, 4, 6-8, 10-12, 15, 40, 41, and 43 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. This rejection is traversed for the reasons set forth below.

The Office alleges that the terms "preselected," "strong antigen," "derived," "allogeneic agent," and "dual specificity lymphocytes" are indefinite. However, as stated in the previous Response to Office Action, filed on June 6, 2003, these terms are, in fact, clear in view of the instant specification. Specifically, the term "preselected" is clear in view of the specification at page 17, lines 12-25, and Examples 7 and 8, for instance. The term "strong antigen" is defined at, for example, page 11, lines 3-7, and page 18, lines 15-16. The term "allogeneic agent" is defined in the instant specification at page 11, lines 7-8, for instance. Although the term "derived" is not defined in the instant specification, it is defined in an online dictionary (www.dictionary.com) as "obtained or received from a source." This term, therefore, is clear in view of the context of the specification (see, for instance, page 30, lines 8-9 of paragraph 79). The term "dual specificity lymphocytes" is described throughout the instant application, and especially, at paragraph 42 on page 11, for instance. The Office further alleges that the phrases "is activated *in vivo* with the strong antigen" and "endogenous T-cell receptor reactive with a preselected strong antigen" are unclear. However, the phrases are, in fact, clear to one of ordinary skill in the art in view of the specification at, for instance, Example 5, and paragraph 53 on page 17, respectively. In order to advance prosecution and not in acquiescence of the rejection, however, the above terms and phrases have been deleted from the pending claims.

The Office further contends that the relationship between the "tumor antigen" and the "strong antigen" are not clear and further asserts that the term "dual specificity lymphocytes" is unclear. Although these terms have been deleted from the pending claims, Applicants would like to take the opportunity to explain to the Office that the lymphocytes of the present invention have *dual* antigen specificity, as they contain *two* antigen-reactive receptors, each of which is reactive with an antigen (e.g., a tumor antigen) or a cell. One receptor is a chimeric receptor or a T-cell receptor, either of which is reactive with a tumor antigen. This receptor allows the present inventive lymphocyte to be targeted to the tumor tissue or cell. The other receptor is a T-cell receptor, which is reactive with a cell, which is allogeneic to the lymphocyte, or an antigen, which is not a tumor antigen. This other receptor induces the present inventive lymphocytes to proliferate, such that there are simply more lymphocytes to attack the tumor tissue or cell. The two receptors of the present inventive lymphocytes recognize two different antigens and, thus, have dual antigen specificity.

The Office contends that the term "tumor antigen" is unclear. However, the specification at, for instance, paragraph 46 on pages 13 and 14, defines this term and gives numerous examples of suitable tumor antigens. Furthermore, in view of the fact that over 54,000 abstracts result from a search of "tumor antigen" in the PubMed

database, the meaning of this term is understood by one of ordinary skill in the art, such that the metes and bounds of the instant invention can be determined. Furthermore, although the specification does not explicitly recite that the normal tissues to which the tumor tissue or cells should be compared should be a matched tissue or cell, i.e., should be of the same tissue or cell type as the tumor tissue or cell, one of ordinary skill in the art recognizes that an antigen is considered a tumor antigen for its increased expression, for example, in comparison to the matched tissue.

The Office argues that the term "allogeneic" is unclear, since this term is a term relative to at least two different things. The pending claims have been amended to recite "a cell, which is allogeneic to the lymphocyte," in order to make it clear that the cell and the lymphocyte are allogeneic to each other.

The Office asserts that it is unclear whether or not "folate binding protein" is an ovarian tumor antigen as elected. However, the specification at, for instance, page 30, 2nd and 3rd lines from the bottom, teaches that the folate binding protein gene is expressed highly on ovarian adenocarcinomas. As one of ordinary skill in the art recognizes that ovarian adenocarcinomas are a type of ovarian tumor, it is, in fact, clear that folate binding protein is an ovarian tumor antigen as elected.

The Office also contends that the term "Mov-γ" in claim 10 is allegedly unclear. Specifically, the Office alleges that the instant specification does not teach the structure of the scFv from Mov18 or the elements combined with the scFv to make the Mov-γ receptor. However, as stated in the last Response to Office Action mailed on June 2, 2003, the instant application incorporates by reference Hwu et al., *JEM* 178: 361-366 (1993); Hwu et al., *Cancer Research* 55: 3369-3373 (1995); both of which further describe Mov-γ. In particular, the former article teaches that the Mov-γ chimeric receptor consists of the V_H and V_L genes of the Mov18 monoclonal antibody, which recognizes FBP, and the γ chain of the FcεR. The γ chain of the FcεR was known in the art, as the nucleotide sequence was published in Kuster et al., *J. Biol. Chem.* 265(11): 6448-6452 (1990). Therefore, contrary to what the Office asserts, the metes and bounds of the term "Mov-γ" can be determined.

Claims 5, 12, 15, and 43 have been cancelled. Therefore, the rejection of these claims under Section 112, second paragraph, is moot.

In view of the foregoing, all of the pending claims meet the requirements of 35 U.S.C. § 112, second paragraph. Therefore, Applicants request that this rejection be withdrawn.

Discussion of the Rejection under U.S.C. § 102(e)

The Office has maintained the rejection of claims 1, 3, 4, 6-8, 10-12, 15, and 40, 41, and 43 under 35 U.S.C. § 102 (e) as allegedly anticipated by U.S. Patent No. 5,830,755 (the '755 patent). This rejection is traversed for the reasons set forth below.

According to the Office, the '755 patent discloses tumor infiltrating lymphocytes from colon adenocarcinoma, transfecting the cells with the chimeric receptor Mov-γ, and recognizing ovarian tumors, and, thus, the present invention is anticipated. However, the '755 patent does not disclose dual specific T lymphocytes in accordance with the present invention. In particular, the '755 patent does not disclose a lymphocyte having *both* of a T cell receptor reactive with a cell, which is allogeneic to the lymphocyte, and a chimeric receptor, which is reactive with a tumor antigen. Furthermore, the '755 patent does not disclose a composition comprising such a lymphocyte, a pharmaceutical composition comprising such a lymphocyte, and a method of preparing such a lymphocyte.

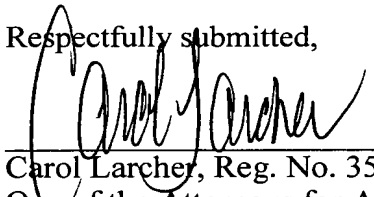
Furthermore, claims 5, 12, 15, and 43 have been cancelled. Therefore, the rejection of these claims under Section 102 (e) is moot.

In view of foregoing, the '755 patent cannot be said to anticipate the present invention. Therefore, Applicants hereby request that the rejection under Section 102(e) be withdrawn.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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